IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Inventors:	**Laughon, Allen S.**
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Examiner:	**Harris, Alana M.**
Customer No.:	**26259**
Group Art Unit:	**1643**
Confirmation No.:	**8778**
Title:	**Compositions and Methods for Negative Regulation of TGF-β Pathways**

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I hereby certify that this paper is being electronically submitted on the date indicated above to the Commissioner for Patents, U.S. Patent & Trademark Office (AF).

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Commissioner for Patents
U.S. Patent & Trademark Office
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REPLY BRIEF

This is in response to the Examiner's Answer dated April 3, 2008, which raised certain issues that Appellant wishes to address.

Regarding the rejection of claims 9-12 under 35 U.S.C. 112, first paragraph, the Examiner alleges at pages 3-4 of the Answer that the specification does not make mention of activin or bone morphogenetic protein signaling influencing transcription. However, Appellant respectfully submits that the claims read on the identification of a "compound that directly interacts with a Smad protein or a Smad protein co-repressor to prevent protein-protein or protein-DNA interactions required for repression of transcription induced by TGF-β, activin or bone morphogenetic protein signaling in cells" [emphasis added]. As such, the claims specifically require transcriptional control by TGF-β, activin or bone morphogenetic protein signaling.

Further, while the Examiner contends that the specification does not support "a promoter which is regulated by a TGF-β, activin or bone morphogenetic protein signal, wherein said cell co-expresses interacting proteins comprising a Smad protein, a DNA binding Smad co-repressor protein and a CtBP protein," absence of a recited term in the Specification is not dispositive so long as the disclosure reasonably supports the limitation. In this regard, it is respectfully submitted that the specification and claims as originally filed provide all the elements required by the claim 9 as currently presented. Indeed, as in step (a) of claim 9, claim 1 as originally filed provides the step of detecting in a cell a first level of transcription in the presence of a Smad protein and a CtBP protein. Original claim 2, which depends from claim 1, further specifies determining transcription levels in presence of a Smad protein, a CtBP protein and a co-repressor protein. As disclosed in the specification at page 7 (lines 24-28) and data presented in Figure 6, these proteins were shown to interact and repress transcription of a lacZ reporter protein under

transcriptional control of the wingless promoter, a promoter which is repressed in response to the decapentaplegic, the *Drosophila* counterpart of activin and bone morphogenetic protein (see page 2, lines 1-7, and page 3, lines 10-13). Thus, based upon disclosure and claims as originally filed, one skilled in the art would conclude that Appellant was in possession of "a promoter which is regulated by a TGF-β, activin or bone morphogenetic protein signal, wherein said cell co-expresses interacting proteins comprising a Smad protein, a DNA binding Smad co-repressor protein and a CtBP protein" as of the filing date. *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

Moreover, while the Examiner suggests that the steps listed in the claims are not of record in the specification, it is respectfully submitted that the claims, as originally filed, are part of the disclosure (MPEP 2163.06 (III)) and support the claims as currently presented. Specifically, claim 1 reads on determining levels of transcription before and after contact of cells with a test compound, wherein said step of determining is carried out in the presence of a Smad protein, a CtBP protein and a co-repressor protein, and wherein a decrease in the level of repression of transcription (*i.e.*, the result of a comparison) is indicative of the ability of the test agent to interfere with transcriptional repression. In so far as the claims as originally filed support the claims as currently presented, the claimed method steps are of record.

Thus, because the claims are fully supported by the whole of the disclosure as originally filed, the Examiner has erred in rejecting claims 9-12 under 35 U.S.C. 112, first paragraph.

With regard to the rejection of claims 9-12 under 35 U.S.C. 112, second paragraph, "[t]he test for definiteness is whether one skilled in the art would understand the bounds of the claim when

read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

As is clear from the whole of the present disclosure, the present invention relates to TGF-β signal transduction pathways which regulate gene expression. In particular, page 2 (lines 1-15) of the specification indicates that

> "TGF-β, and its related factors including activin, bone morphogenetic proteins (BMPS), and their *Drosophila* counterpart, decapentaplegic, each signal to their target cells by a unique signaling cascade activated by ligand-induced serine/threonine kinase receptor complex formation… It is now well established that TGF-β signaling pathways switch target genes on through the activities of Smad proteins. These cytosolic proteins are recruited and phosphorylated by the TGF-β, activin, or BMP receptor complexes. Smad proteins exist as monomers in unstimulated cells but homo- or hetero-dimerize and translocate to the nucleus of the cells where they then activate target gene expression through contact with cofactors and DNA."

It is quite clear from this passage that bone morphogenetic protein, as well as TGF-β, activin, and decapentaplegic are signals which form receptor complexes that modulate phosphorylation of Smad proteins thereby regulating target gene expression. Based upon this disclosure, one skilled in the art would understand the bounds of a bone morphogenetic protein signal when read in light of the

specification. Therefore, the Examiner has erred in rejecting claims 9-12 under 35 U.S.C. 112, second paragraph.

Respectfully submitted,

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